the specification teaches on pg. 5 and in Fig. 21 that a primary tumor taken from a patient already suffering with multiple auxiliary lymph node metastases exhibits staining for CD3 and beta F1 and further teaches that metastatic tumor cells taken from another patient exhibited staining for CD3 and beta F1. It thus appears that the Examiner is grounding this enablement rejection on a lack of utility of the claimed invention.

What the examiner is saying is required to show utility and thus enablement amounts essentially to the equivalent of a phase II trial requiring rigorous clinical testing procedures with the patients being followed for as much as 5 years or longer. Applicant respectfully disagrees. As stated at MPEP 2107(IV), a 35 USC 112, first paragraph, rejection grounded on a lack of utility basis should not be imposed unless a 35 USC 101 rejection is proper. All that is necessary for 35 USC 101 and thus for enablement under 35 USC 112, first paragraph, grounded thereon is that the evidence, considered as a whole, lead a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. See MPEP 2102.02, 2164.07(I)(C), and 2107(VII). There is abundant clinical and experimental evidence in the specification along with work of others described in the specification (or otherwise in the literature) which would lead a person of ordinary skill in the art to conclude that it is more likely than not true that a tumor will metastasize when one or more of the T-cell markers are present and will not metastasize when the T-cell markers are not present, evidence which is corroborated by a plausible theory which is discussed in the specification, i.e., that the acquisition of lymphotropic metastasis by cancer cells is accompanied by their ability to express aberrant lymphoid specific genes or their products, i.e., a relation between T cells (which are always migratory) and cancer cells which become metastatic (invasive cancer cells which

become migratory). See page 1, last full paragraph, of the specification.

The discussion on pg. 5 and in Fig. 21 discussed by the Examiner in the Office Action constitute only a small part of the evidence of usefulness of the present invention. This discussion is provided to show that there was no significant difference between primary and metastatic tumors in two breast cancer patients and corroborates the other findings discussed in the specification. Applicants' more important clinical and experimental evidence, including before and after data, relating to the present issue was summarized in the Amendment mailed June 23, 2000, and is discussed again hereinafter.

The following experimental data demonstrating an interval of time between expression of a T-cell antigen and the metastatic event relies on testing on a human cell line, SW480, from a primary tumor (before), and its related cell line, SW620, which is from a metastasized tumor in the same patient a year later (after), and clones or subsets SW480E (has high metastatic potential) and SW480R (has low metastatic potential). See the paragraph which spans pages 10 and 11 of the specification. Also see Yoon et al, Abstract 3638, *Proceedings of the American Association for Cancer Research*, vol. 38, p. 542, March, 1997 (copy enclosed with the prior Amendment) wherein it is stated that the results of their study suggest that, even though the R-type (SW480R) cells are more tumorigenic, E-type (SW480E) cells are more invasive and metastatic. The clones SW480E and SW480R are thus from the tumor SW480 before it was found to have metastasized a year later. Thus, a finding of a T-cell antigen in either of these clones, as discussed hereinafter, would show that the T-cell antigen was in the tumor before it was later found to have metastasized, i.e., a before and after event.

Fig. 9 (see discussion thereof on page 11, first full

paragraph, of the specification) contains data which shows that TCRβ (CTβ) was detected in the cloned tumor cell line, SW480E, which is metastasizing, and the amount detected was greater than the amount detected in the cloned tumor cell line, SW480R, which is nonmetastasizing, thus showing experimentally that, although TCRβ may sometimes be found in nonmetastasizing tumors, still the presence of TCRβ in cancer cells may be a high predictor of metastasis. Moreover, the presence of TCRβ in either clone shows that TCRβ was in the primary tumor SW480 before it was later found to have metastasized, i.e., a before and after event.

Table 3 on page 20 of the specification contains data from experiments with Wistar Furth rats which shows that all of those primary breast cancer tumors (MT-449, MT-450, SMT-2A, and TMT-081) which were found to have cells expressing either CD4 or CD8 were found to be capable of metastasizing while all 6 tumors in which no CD4 or CD8 was found were nonmetastasizing. See page 10, first full paragraph, of the specification. This data thus show experimentally that the presence of CD4 or CD8 in cancer cells may be a good predictor of metastasis. Thus, primary tumors before metastasizing were found to contain either CD4 or CD8, while the nonmetastasizing primary tumors were found not to contain either CD4 or CD8, i.e., a before and after event.

Fig. 18 and Table 5 on page 22 of the specification (see the first two full paragraphs on page 13 of the specification) contain experimental data which shows that ZAP-70 was found to be present in the SW480E cells, which are metastasizing, while little or none was found in the already metastasized cells, SW620, and that none was found in SW480R cells, which are nonmetastasizing, thus showing experimentally that the presence of ZAP-70 in cancer cells may be a good predictor of metastasis. Moreover, the presence of ZAP-70 in either clone shows that ZAP-70 was in the primary tumor SW480 before it was later found to

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have metastasized, i.e., a before and after event.

Table 6 on page 23 of the specification shows the presence or absence of the T-cell products CD3, CD4, CD8, and TCRβ (CTβ) in fresh human breast cancer cells 13 of which had no lymph node involvement and were thus believed likely to be nonmetastasizing and 7 of which had lymph node involvement and were thus considered to be metastasizing. As seen in Table 6, with only an exception for one nonmetastasizing tumor wherein the presence of CD8 was positive and the presence of CD4 was borderline, none of the T-cell products CD3, CD4, CD8, and TCRβ (CTβ) was detected in any of the other 12 nonmetastasizing tumors and one or more of the T-cell products CD3, CD4, CD8, and TCRβ (CTβ) was detected in each of the 7 metastasizing tumors. The absence of the T-cell products CD3, CD4, CD8, and TCRβ in the tumors which had no lymph node involvement (with one exception) as a predictor of future nonmetastasis is consistent with the lack of lymph node involvement as an indicator of future nonmetastasis, i.e., a before and after event, and the presence of T-cell antigens in the tumors with lymph node involvement is consistent with the presence thereof being a predictor of future metastasis.

These clinical and experimental findings are consistent with findings in the literature such as Kim et al (Kim being one of the Applicants of the present application), *Proc. Am. Assoc. Cancer Res.* 34:63A (1993), discussed on page 6 of the specification, wherein primary nonmetastatic non-lymphoid mammary rat tumor cells (which did not express T-cell markers) were successfully converted into metastatic tumor cells that carry TCR associated molecules by fusing them with thymocytes, i.e., a man-made before and after event. Other literature by other authors consistent with the clinical and experimental findings is discussed on page 6, the 2 full paragraphs, and the paragraph which spans pages 6 and 7, of the specification.

The clinical and experimental findings as well as the findings of others as expressed in the literature are consistent with Applicants' theory on which the present invention is based, i.e., that primary nonmetastatic tumors are convertible into metastatic tumors by lymphoid genes possibly by fusion (as in the above Kim et al reference) or by derepression or emperiopoiesis, as also discussed on pages 6 and 7 of the specification.

It is respectfully submitted that the clinical and experimental findings (which do provide ample before and after data) together with the literature and the theory of the present invention, considered as a whole, would lead a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true, which is the standard therefor as discussed in MPEP 2164.07(I)(C) and 2107(VII). See also MPEP 2102.02.

It is of course expected that the present promising invention will require further research and development and clinical trials before it can become part of accepted medical practice. However, it is respectfully submitted that usefulness and therefore enablement has been adequately shown to the degree required by the patent law, i.e., that the invention, considered as a whole, would lead a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir., 1995), and quoted at MPEP 2107(III):

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II trials in order to prove utility, the associated costs would prevent many companies from obtaining

patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many critical areas such as the treatment of cancer.

The specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. Therefore, it is respectfully requested that the rejection be withdrawn.

It is therefore respectfully submitted that this application is in condition for allowance, and such is respectfully requested.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning at line 21 on page 5 has been amended as follows:

Fig. 21 is a view of immunocytochemical and fluorescence photomicrograph analysis of TdT, CD3 and βF1 on stage II and stage III human breast ductal carcinoma cells in two women ~~woman~~. **A)** Tumor cell imprints made from 18 mm primary tumor of a 44-year old woman (MB/87-4906) with multiple axillary lymph node metastases (15 positive lymph nodes out of 21) show many TdT-positive cells as demonstrated by PAP procedure. These cells were also positive for CD3ε and βF1 (anti-CTβ). **B)** Metastatic tumor cells from an enlarged axillary lymph node of a 82-year-old woman (EN/88-279) (three massive metastatic axillary lymph nodes) who ~~ho~~ had a large primary tumor (50 mm diameter) fixed to the chest wall, showed scattered TdT-positive cells as demonstrated by the indirect immunofluorescence procedure. Metastatic tumor cells from the second patient (EN/88-279) expressed **C)** CD3ε and **D)** βF1 (anti-CTβ) (X800). **There was no significant difference in the number and intensity of CTβ and other T cell associated molecules between primary and metastatic tumors in these breast cancer patients.**--